UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY, Plaintiff,	)	
vs.	)	1:06-cv-1017-SEB-JMS
TEVA PHARMACEUTICALS USA, INC., Defendant.	)	

ENTRY ON CLAIM CONSTRUCTION

This matter comes before the Court for construction of certain patent terms relevant to the underlying infringement action. Plaintiff, Eli Lilly and Company ("Lilly"), and Defendant, Teva Pharmaceuticals USA, Inc. ("Teva"), each presents the Court with proposed constructions for nine disputed terms found in three Lilly patents relating to the formulation of Lilly's EVISTA® drug. We conducted a Markman hearing on March 17, 2008, at which the parties presented evidence, testimony, and oral argument as to the proper construction of the disputed terms. Having considered those presentations as well as the parties' briefings in this matter, we now enter the following factual and legal findings relating to the construction of the disputed patent language.

Factual Background

Lilly and Teva are both companies involved in the formulation and manufacture of

pharmaceuticals. This case concerns seven patents[1] related to Lilly's EVISTA® drug (raloxifene hydrochloride, or "raloxifene"), which is used to treat postmenopausal osteoporosis. Lilly asserts that an Abbreviated New Drug Application ("ANDA") filed by Teva with the FDA for the manufacture and sale of raloxifene infringes upon the seven named Lilly patents. Lilly brought this action against Teva on June 29, 2006.

EVISTA® is indicated for the treatment and prevention of postmenopausal osteoporosis. Lilly Br. at 1. The active ingredient in EVISTA® is raloxifene, a chemical substance in powder form. The patents at issue for purposes of claim construction relate to the size of the raloxifene particles within the drug. Lilly's discovery, presented in the particle size patents, is that raloxifene particles that are within a particular size range have desirable, consistent dissolution and bioavailability characteristics, as well as characteristics that improve manufacturing capabilities. '811 Patent, col. 3, lns. 15-23.

The nine disputed claim constructions at issue here can be characterized into three groups. The first concerns pharmaceutical *excipients* – inactive ingredients combined with raloxifene to produce a dosage form. The second category concerns the definition to be applied to the term *"size"* and *"mean particle size"* as they appear in the patent. Finally, the parties ask us to construe terms involving the word *"about"* as that word

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[1] The patents under dispute are: U.S. Patent No. RE39,050 (the '050 patent); U.S. Patent No. RE38,968 (the '968 patent); U.S. Patent No. RE39,049 (the '049 patent); U.S. Patent No. 6,906,086 (the '086 patent); U.S. Patent No. 6,458,811 (the '811 patent); U.S. Patent No. 6,797,719 (the '719 patent); and U.S. Patent No. 6,894,064 (the '064 patent).

For present purposes, all the disputed terms requiring construction appear in the '811, '719, and '064 patents (the "particle size patents").

applies to measurement variability of particle size.

Legal Analysis

I. Claim Construction Principles

Claim construction is a "fact-dependent, invention-oriented exercise in logic and law[]" (SmithKline Beecham Corp. v. Apotex Corp., 438 F.3d 1312, 1322 (Fed. Cir. 2006)), which requires us to determine, as a matter of law, how the scope and meaning of each disputed claim is to be construed. See Markman v. Westview Instruments, Inc., 517 U.S. 370 (1996). As the scope of a claim "is necessarily determined by the language of the claim, claim construction must begin with these words." Dow Agrosciences LLC v. Crompton Corp., 381 F. Supp. 2d 826, 831 (S.D. Ind. 2005) (Barker, J.). Absent an express intent otherwise, claim terms should be given "the ordinary and customary meaning . . . that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." Phillips v. AWH Corp., 415 F.3d 1303, 1313 (Fed. Cir. 2005).[2]

In looking principally to the intrinsic evidence – which includes the claim language itself, written specifications, and the prosecution history – courts may obtain an "objective baseline from which to begin claim interpretation." Id.; Panduit Corp. v. HellermannTyton Corp., 451 F.3d 819, 829 (Fed. Cir. 2006). Among all types of intrinsic

[2] Decisions of the Federal Circuit regarding substantive matters of patent law are binding on federal district courts. See Murata Mfg. Co. v. Bel Fuse, Inc., 422 F.Supp.2d 934, 938 fn. 4 (N.D. Ill. 2006); Midwest Industries, Inc. v. Karavan Trailers, Inc., 17 F.3d 1356, 1359 (Fed. Cir. 1999).

evidence, courts have indicated that the specification "is the single best guide to the meaning of a disputed term." Vitronics, Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996). In the specification, "the patentee must provide a written description of the invention that would allow a person of ordinary skill in the art to make and use the invention." Centillion Data Systems, LLC v. Convergys Corp., 529 F.Supp.2d 982, 989 (S.D. Ind. 2008) (citations omitted). Thus, to correctly construe disputed claim terms, the Court must refer to the specification's description of the invention. In sum, as the Federal Circuit recently explicated in Phillips v. AWH Corp.:

> Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim. The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.

415 F.3d at 1316 (quoting Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1250 (Fed. Cir. 1998)).

Extrinsic evidence, such as dictionaries and treatises, may also be used to assist the court in construing the claim's meaning, but such evidence is afforded less legal significance than that from intrinsic sources. C.R. Bard, Inc. v. U.S. Surgical Corp., 388 F.3d 858, 862 (Fed. Cir. 2004). Additionally, "if the meaning of the claim term is unambiguous, and the court can determine that meaning from the intrinsic evidence, it need not rely on extrinsic evidence in construing the claim." Dow Agrosciences, 381 F. Supp. 2d at 832 (citing Vitronics Corp., 90 F.3d at 1583). Further, extrinsic evidence

which contradicts the intrinsic record of the claim must be disregarded. Markman, 52 F.3d at 981.

II. Claims Related to Pharmaceutical Excipients

The first set of disputed claims concerns pharmaceutical excipients – inactive ingredients combined with the raloxifene particles to produce a usable dosage form. Sub-classifications of excipients include *surfactants*, surface active agents which reduce surface tension, and *diluents*, which work as "fillers" to increase the bulk of a formulation.[3] The patents[4] contain two disputed phrases related to excipients:

Disputed Term	Lilly's Construction	Teva's Construction
surfactant	A compound that reduces the surface tension of liquids, or reduces interfacial tension between two liquids or a liquid and a solid.	A substance identified as a surfactant in the Handbook of Pharmaceutical Excipients.
water-soluble diluent	A pharmaceutically inert substance, capable of being dissolved in water, that increases the bulk of a tablet.	A substance identified as a diluent in the Handbook of Pharmaceutical Excipients that is soluble in water, as classified by the USP.

There does not appear to be a genuine dispute that Lilly's functional definitions of these two terms accurately represent the ordinary meanings of the terms. See, e.g., Pl.'s

[3] The term at issue in the patents is "water-soluble diluent" – that is, of course, a diluent which is soluble in water.

[4] These terms are found in both the '719 and '064 patents.

Ex. 7 (Handbook of Industrial Surfactants excerpt describing "surfactants"); Pl.'s Ex. 15 (testimony of Teva's expert, Dr. Arthur Kibbe, in other litigation, regarding the definition of "surfactant"); Pl.'s Ex. 4 (Remington: The Science and Practice of Pharmacy excerpt describing "diluents"). Rather, the dispute centers on whether a functional definition (i.e., the ordinary meaning of the terms to a person of ordinary skill in the art) or a definition obtained by reference to an extrinsic source is preferable.

Lilly asserts that its proposed constructions are preferable because Teva's proposed constructions are contradictory to the patent specifications. For example, the '811 patent specification identifies cetyl alcohol, polysorbate 80, and glycerol monostearate as exemplary surfactants. See '811 patent, col. 31, lns. 12-26 ("Examples of excipients . . . that are suitable for . . . formulations [of the present invention] include the following: . . . surface active agents such as cetyl alcohol, polysorbate 80, [and] glycerol monostearate[.]"). However, Lilly demonstrates that the Handbook of Pharmaceutical Excipients does not list cetyl alcohol or glycerol monostearate as "surfactants" in its index.[5] See Pl.'s Ex. 6 (Handbook of Pharmaceutical Excipients, 5th ed. (2006), p. 914).

Teva (and its expert, Dr. Kibbe) argue that Lilly's proposed constructions are

[5] Lilly states that cetyl alcohol is an emulsifying agent (a type of surfactant), and glycerol monostearate is an emulsifying and solubilizing agent. Lilly Brief [Docket No. 154] at 8. Further, solubilizing agents are cross-referenced in the index of the Handbook of Pharmaceutical Excipients under "surfactants," but it is not clear from the evidence presented whether this serves to "identify" such substances as surfactant pursuant to Teva's proposed definition. These vaguenesses further support our holding that Lilly's functional definition is preferable.

overly broad, unhelpful dictionary definitions, and that Teva's proposed constructions reflect the method a pharmaceutical formulator would actually use in determining if a substance in a formulation were a surfactant: that is, he or she would look it up in the Handbook of Pharmaceutical Excipients. See Def.'s Ex. D (Kibbe Report) at ¶ 34. Teva maintains that Lilly's definitions are unworkable because under Lilly's proposed constructions, "a competitor cannot determine whether its formulation meets the 'surfactant' requirement without testing every ingredient to see whether one of them has some ability (however slight) to reduce surface tension." Teva Brief at 24.

We adopt Lilly's proposed constructions for the terms "surfactant" and "water-soluble diluent." As we have discussed in detail above, intrinsic evidence (such as the patent specification) is the primary baseline from which we begin to interpret the patent claim; Teva's constructions, which rely entirely upon extrinsic sources (and for that matter, a source published ten years after the patent specification was filed) are thus disfavored in comparison to the intrinsic evidence provided within the patent itself. Further, as Lilly points out, Teva's proposed constructions are inconsistent with the limitations contained within the patent specifications. See MBO Labs, Inc. v. Becton, Dickinson & Co., 474 F.3d 1323, 1333 (Fed. Cir. 2007) ("[A] claim interpretation that excludes a preferred embodiment from the scope of the claim is rarely, if ever, correct.") (quoting On-Line Techs., Inc. v. Bodenseewerk Perkin-Elmer GmbH, 386 F.3d 1133, 1138 (Fed. Cir. 2004)).

Thus, for the foregoing reasons, we conclude that the proper construction of

"surfactant" is "a compound that reduces the surface tension of liquids, or reduces interfacial tension between two liquids or a liquid and a solid," and the proper construction of "water-soluble diluent" is "a pharmaceutically inert substance, capable of being dissolved in water, that increases the bulk of a tablet."

III. Claims Related to the Terms "Size" and "Mean Particle Size"

The second category of disputed claims concerns the terms "size" and "mean particle size," both of which are found in the '811, '719, and '064 patents in reference to the raloxifene particles. As we have explained, the size of the raloxifene particles is of core importance to Lilly's invention. The patents at issue reference[6] (and the parties are in agreement) that the method to be used to measure the size of the raloxifene particles is the *laser light diffraction scattering* method. Using this method, a laser beam is passed through a sample containing raloxifene particles; when the beam hits the particles, it causes some of the light to diffract. The intensity and angle of the diffracted light can be used to measure the size of the particles. Pl.'s Ex. 9 (Richard Karuhn expert report) ¶¶ 13-16.

The parties dispute the proper construction of these terms as follows:[7]

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[6] See, e.g., '811 patent, col. 4, lns. 14-16.

[7] Emphasis has been added to Lilly's proposed constructions to underscore the core disagreement between the parties as to the construction of these terms..

Disputed Term	Lilly's Construction	Teva's Construction
size	The equivalent spherical volume diameter as determined by laser light diffraction scattering *using an appropriately prepared sample*.	The equivalent spherical volume diameter of a particle as determined by laser light diffraction scattering.
mean particle size	The mean of the equivalent spherical volume diameter as determined by laser light diffraction scattering *using an appropriately prepared sample*.	Mean equivalent spherical volume diameter by laser light diffraction scattering.

The '811 patent explicitly states that "[t]he term 'mean particle size' is defined as equivalent spherical diameter as determined by laser light diffraction scattering." '811 patent, col. 4, lns. 14-16. The core disagreement between the parties, then, is whether the phrase "using an appropriately prepared sample" should be appended to this specification. Lilly maintains that it should, arguing that "appropriate same preparation is necessary for the proper characterization of particle size using laser light diffraction scattering" (Pl.'s Ex. 9 ¶ 18). If a sample is not prepared correctly, individual raloxifene particles may agglomerate into "clumps," which will skew the size measurements to make the particles appear larger than they actually are. Id. Agglomeration can be avoided by properly preparing the sample through selection of an appropriate suspension carrier fluid to help separate the particles, and through agitation of the sample. Id. ¶ 19. Indeed, the patent specification provides specific instructions for proper preparation of the raloxifene suspension sample to obtain accurate particle size readings. See '811 patent, col. 23 ln.

44 - col. 24 ln. 21.

Teva rejoins that Lilly's proposed added language is unnecessary and inappropriate. It asserts that Lilly "improperly seeks to import a limitation that appears nowhere in the claim itself or the '811 specification." Teva Brief at 6. Further, as Teva points out, Lilly's own expert, Mr. Karuhn, testified in his deposition that appropriate preparation of the sample "goes without saying. I don't think you need to put it in there." Def.'s Ex. M (Karuhn Dep.) at 77 lns. 4-5.

Here, we agree with Teva: the "using an appropriately prepared sample" language is superfluous, and we decline to include it in our constructions here. Claim construction is intended to "elaborat[e] the normally terse claim language in order to understand and explain . . . the scope of the claims." Terlep v. Brinkmann Corp., 418 F.3d 1379, 1382 (Fed Cir. 2005) (internal quotation marks omitted). It should not be "an obligatory exercise in redundancy." O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., 521 F.3d 1351, 1362 (Fed. Cir. 2008) (quoting U.S. Surgical Corp. v. Ethicon, Inc., 103 F.3d 1554, 1568 (Fed. Cir. 1997)). The inclusion of Lilly's proposed language regarding appropriate preparation of the sample is akin to adding language saying "if you do it right"; in our view, proper preparation of the sample is presumed, and the proposed additional language does nothing to aid our understanding of the disputed terms. Any dispute about whether a sample has actually been properly prepared is more appropriately resolved on the merits, rather than in the claim construction stage. Thus, we adopt Teva's proposed

constructions of these two terms.[8]

IV. Claims Related to Measurement Variability and the Term "About"

The measurement of particle sizes by laser light diffraction scattering is subject to variability. The third (and most hotly contested) set of claim terms in dispute concerns the allowable degree of variability among particle size measurements.[9] Lilly's patents use the word "about" to reflect the range of measurement variability to be reasonably expected. Lilly and Teva dispute what range of values is denoted by the term "about."

The word "about" appears in two separate disputed contexts in the Lilly patents. The first concerns measurements of a *mean* particle size value for a sample, and reflects the fact that different measurements of the mean (average) particle size of a sample are expected to vary somewhat around the "true" mean value for that sample. See, e.g., '811 patent, col. 3, lns. 24-26 ("The mean particle size of the compounds of formula I, as set

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[8] We note that, besides the "appropriately prepared sample" clause, there are very slight differences in wording between Lilly's and Teva's proposed constructions of these two terms. Lilly has not expressed a dispute about these slight wording differences, and they do not appear to us to be material.

[9] Initially, we note Lilly's contention that it is unnecessary for us to construe this set of disputed claim limitations at this point in the litigation, on the basis that "proof of whether a particular measured value offered in evidence is or is not within the reasonably expected range of variability in the measurement process is appropriately left for factual proof at trial. . . . Teva's request to evaluate this issue in the context of hypothetical measured values divorced from an actual measurement is really an inappropriate request for an advisory opinion." Lilly Brief at 14-15. We disagree with Lilly's assertion and opt to consider the term "about" in the claim construction context. Compare Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211, 1217 (Fed. Cir. 1995) ("The determination of whether the literal meaning or scope of '*about* 5:1 to *about* 7:1' includes 4:1 is a matter of claim construction, a question of law[.]") (emphasis added).

out by the invention, is less than about 25 microns, preferably between about 5 and about 20 microns.") The second type of usage refers to the amount of *variability* in the particle distribution (i.e., the width, or spread, of the distribution). Certain portions of the disputed patents claim that ninety percent of a given particle sample must be smaller than "about" a particular size measurement.[10] See, e.g., '811 patent, col. 3, lns. 1-3 ("[T]he present invention encompasses compounds of formula I wherein at least 90% of the particles have a particle size of less than about 50 microns[.]").

The parties each propose a statistical method to determine the range of acceptable values denoted by "about." Application of the parties' respective methodologies yields the values denoted in the table below:

Disputed Term	**Lilly's Construction**	**Teva's Construction**
less than about 25 microns	The term "about" means values within the reasonably expected range of variability in the measurement process. Accordingly, the phrase "less than about 25 microns" as used in the context of the claims means: a measured value of less than **30.1** microns.	Less than **26.3** microns.

[10] The parties sometimes refer to this measurement as the "90% less than," "x_{90}," or "d90" value.

less than about 50 microns	The term "about" means values within the reasonably expected range of variability in the measurement process. Accordingly, the phrase "less than about 50 microns" as used in the context of the claims means: a measured value of less than **67.4** microns.	Less than **50.4** microns.
between 5 and about 20 microns	The term "about" means values within the reasonably expected range of variability in the measurement process. Accordingly, the phrase "between 5 and about 20 microns" as used in the context of the claims means: a measured value between 5 microns and **24.1** microns.	Between 5 microns and **21.3** microns.
between about 5 and about 25 microns	The term "about" means values within the reasonably expected range of variability in the measurement process. Accordingly, the phrase "between about 5 and about 25 microns" as used in the context of the claims means: a measured value between **4.0** microns and **30.1** microns.	Between **3.7** microns and **26.3** microns.

between about 5 and about 20 microns	The term "about" means values within the reasonably expected range of variability in the measurement process. Accordingly, the phrase "between about 5 and about 20 microns" as used in the context of the claims means: a measured value between **4.0** microns and **24.1** microns.	Between **3.7** microns and **21.3** microns.

Lilly's Proposed Construction

Lilly proposes that the proper method for calculating the allowable degree of measurement variability involves the statistical concepts of coefficients of variation ("CV") and confidence intervals. The CV (computed as the standard deviation divided by the mean) is a statistical value which measures the spread of data around a given value, while taking into account the fact that variability increases as the measured value increases. See Edison Elec. Institute v. EPA, 391 F.3d 1267, 1271 fn. 4 (D.C. Cir. 2004) (explaining that the CV "measures the extent to which multiple measurements tend to depart from their average value. The greater the CV, the less precise the measurement."); see also Astra Aktiebolag v. Andrx Pharaceuticals, Inc., 222 F. Supp. 2d 423, 494 n. 39 (S.D.N.Y. 2002) (describing the CV as "[b]asic statistical analysis"); Pl.'s Ex. 12 ¶ 14. Lilly further cites the testimony of its expert, Dr. Ronald Thisted, in support of the use of the CV as a "common measure used to describe the amount of variability" of a sample. Pl.'s Ex. 12 ¶ 14.

The United States Pharmacopeia ("USP"), a standard pharmaceutical reference

cited by both parties,[11] describes use of the CV with specific reference to laser light diffraction scattering, and further designates particular values deemed appropriate for use: "[F]or any central value of the distribution, for example the median (x_{50}), the coefficient of variation is less than 10%. For values away from the center of the distribution, for example x_{10} and x_{90}, the coefficient of variation cannot exceed 15%." Pl.'s Ex. 14 (USP excerpt) at 165. Further, Lilly argues, values disclosed in the patent suggest a CV value around the median that is consistent with the USP standard.[12]

Lilly's expert, Dr. Thisted, explains that the accuracy of a particle size measurement is also limited by the variability inherent in the measurement process. Pl.'s Ex. 12 ¶ 13. This uncertainty is accounted for by the *confidence interval*. A confidence interval illustrates the reasonably expected range of variability in measurement. See Ortho-McNeil Pharmaceutical, Inc. v. Kali Labs., Inc., 482 F.Supp.2d 478, 495 (D. N.J. 2007) ("Each . . . [measured] value is only a statistical estimate, based upon the experimental data, of what the *true* . . . value would be if it were possible to [run an infinite number of measurements]. . . . To represent this uncertainty, [the confidence

[11] See, e.g., Pl.'s Ex. 13 (Kibbe report) at ¶ 24 (describing the USP as "the official compendia of pharmaceutical products and ingredients").

[12] The patent discloses that "[m]ultiple runs of [a] control sample [having particles within the expected size range] established the standard deviation in measurement of the mean to be 1.3 microns." '811 patent, col. 23, lns. 50-52. This measurement divided by the mid-point of the "expected range" (12.5 microns, which Mr. Karuhn maintains that in his expert opinion "would have been understood, based on the disclosure of the patent" to be the mean particle size of the control sample (Pls.' Ex. 30 ¶ 2)) yields a CV of 10.4%. Lilly asserts that this figure is consistent with the 10% USP protocol, and with Lilly's contemporaneously reported CV submitted to the FDA, which provided that the CV should be less than 14% for mean values. Pls.' Ex. 10 at EV 111 1756.

interval is used]. A confidence interval describes the variation in the estimate by using upper and lower values that represent a possible range of values that could be obtained from repeated experiments.") (internal quotation marks omitted). Lilly also cites the testimony of Teva's expert, Dr. Sanford Bolton, in another pharmaceutical patent case, employing confidence intervals in his interpretation of the term "about." See Ranbaxy Labs. Ltd. v. Abbott Labs., 2005 WL 3050608, at *24 (N.D. Ill. Nov. 10, 2005).

Lilly asserts that a 95% confidence interval is standard in the pharmaceutical industry and proper in our construction of the claim here. Pl.'s Ex. 12 (Thisted report) ¶ 15; Pl.'s Ex. 19 (USP excerpt) at 1712. This means that 95 percent of the time, the true mean value will be contained within the lower and upper limits[13] of the confidence interval range.

Lilly, then, proposes that the term "about" should be interpreted to encompass values within the range of a 10% CV of the mean value, applied in the context of a 95% confidence interval.[14] For the 90th percentile figure of the particle size distribution, Lilly proposes essentially the same method of constructing the term "about," except that a 15% CV (rather than the 10% CV at the mean) is used. Lilly asserts that this value is within the allowance permitted by USP protocol for particles at the 90th percentile, as well as

[13] These limits fall, respectively, 1.96 standard deviations below and above the mean. Pl.'s Ex. 12 ¶¶ 15-16. 1.96 is thus the "confidence factor" multiplier that corresponds to a confidence interval of ninety-five percent.

[14] Thus, Lilly's computation of the reasonably expected variation for a mean value is the CV [.15] times the mean times the confidence factor [1.96].

Lilly's contemporaneously submitted FDA particle size protocol, which allowed for a CV of 18% at the 90th percentile point. Application of this methodology yields the values denoted in the table *supra*.

Teva disputes Lilly's proposed constructions on several fronts. First, it invokes the principle of claim construction (discussed *supra*) that in construing a claim term, a court may not rely on extrinsic evidence that contradicts the intrinsic evidence, including the patent specification. See On-Line Techs., Inc., 386 F.3d at 1139 (Fed. Cir. 2004) ("Extrinsic evidence . . . cannot be used to alter a claim construction dictated by a proper analysis of the intrinsic evidence."). Teva argues that the CV methodology is not disclosed in the patent specification or prosecution history, and thus relies upon inappropriate extrinsic evidence.

Second, Teva argues that Lilly's methodology, which employs a constant CV value in determining the allowable amount of measurement variability for a given value and further broadens the allowable size range by application of a confidence factor, is flawed. Among Teva's criticisms is that the range proposed by Dr. Thisted for the 90th-percentile value contradicts the '811 patent specification in that it would include a sample that the patent discloses is *outside* the claimed size range.[15] Teva further argues that the

[15] Teva's criticism hinges on the '811 patent's discussion of Lilly's "ball milled bulk lot #3." '811 patent, col. 25, table 6. The d90 value listed for this lot is 55.3 microns, which fits within Lilly's proposed construction of "less than about 50 microns" for the d90 value, but outside Teva's proposed construction. Teva asserts that, as disclosed by the '811 patent, ball milled bulk lot #3 did not have desired dissolution and absorption characteristics, and thus the d90 value of 55.3 microns should not be covered by the patent. Teva Br. at 15 (discussing '811 (continued...)

12.5 micron mean particle size referred to by Lilly as the midpoint of the control sample (which Lilly uses to corroborate its proposed 10% CV at the mean) is "unsupported and speculative." Teva Br. at 12. The patent does not explicitly disclose the mean particle size for the control sample, and Teva argues that a person of ordinary skill reading the patent would not know what that value was; accordingly, Teva maintains that we should reject Lilly and Dr. Thisted's CV analysis.[16]

Teva also maintains that, even if a confidence interval is used to figure the allowable degree of measurement variability, the two-sided, 95% confidence interval proposed by Lilly and Dr. Thisted is inappropriate. Rather, Teva (and its expert, Dr. Bolton) propose use of a one-sided 90% confidence interval, arguing that one need not determine the allowable variance on *both sides* of the value given in the patent. Teva Br. at 23; Def.'s Ex. G (Bolton expert report) ¶ 24. However, Lilly introduces evidence that

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[15](...continued)
patent, col. 26, lns. 3-16). At the Markman hearing, Lilly countered that the lot in question is *not* excluded from the particle size ranges claimed in the '811 patent, and that the portions of the patent discussed by Teva refer to *bulk* (unformulated) raloxifene. Lilly maintains that there is no data in the patent demonstrating that dissolution is not uniform when the raloxifene is formulated into tablet form.

[16] Lilly's expert, Richard Karuhn, counters that "[v]alidations with control samples of the type referenced in the '811 patent were and are typical for particle size measurement of fine particles using laser light diffraction scattering. . . . [I]t was and remains the standard practice . . . where a single control sample is used, to use a control sample having a mean particle size corresponding as closely as possible to the midpoint of the expected mean particle size range. Based on this custom and practice, it would have been understood that the [mean particle size of the] single control sample [described in the '811 patent] . . . would correspond to the midpoint of [the expected size] range, i.e., between 12 and 13 microns." Pl.'s Ex. 30 (Karuhn report) ¶¶ 3-5. Mr. Karuhn, who has 35 years of experience in fine particle technology, further testified that commercial standards of this size were available during the relevant time period. Id. ¶ 6.

the FDA has an express preference for a two-sided 95% confidence interval, and that Teva's expert, Dr. Bolton, has recognized in other contexts that regulatory agencies typically prefer two-sided statistical tests. Pl.'s Exs. 27, 28, 67. In our view, Teva has not presented any evidence which controverts these statements or otherwise persuades us that use of the two-sided 95% confidence interval is not what a person of ordinary skill in the art would employ.

Teva further argues that Dr. Thisted lacks relevant expertise and is unqualified to opine about pharmaceutical formulation, as he is not a person of ordinary skill in the art to which the patent is directed; Dr. Thisted is a statistician at the University of Chicago and is not specifically an expert in pharmaceutical formulation. Teva relies upon Dr. Thisted's deposition testimony that a person with a background in pharmaceutical formulations "would not require consultation with someone with an advanced degree." Def.'s Ex. L at 13.

Teva's Proposed Construction

Teva maintains that the term "about" should reflect measurement values within one standard deviation of the specified value, arguing that such an approach is explicitly disclosed in the patent specification. In support of this construction, Teva provides the expert testimony of Dr. Kibbe that a person skilled in pharmaceutical formulation would consider such an approach reasonable, and that Lilly's statistical approach is overly technical, convoluted, and "unreasonably stretches the claimed size values." Teva Br. at

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As we have explained above, the '811 patent discloses that, using the laser light scattering technique, specified equipment, and "a control sample having particles within the size range expected[,] . . . [m]ultiple runs of the control sample established the standard deviation in measurement of the mean to be 1.3 microns." '811 patent, col. 23, lns. 45-53. Teva maintains that 1.3 microns of variability is thus the expected degree of measurement variability denoted by the term "about" with respect to measurements about a mean; in other words, "when calculating a mean particle size value for any given sample, a person skilled in the art would expect the measured value to fall within 1.3 microns of the actual value." Teva Br. at 9, Defs.' Ex. D (Kibbe Report) ¶ 28. Teva further argues that this amount of variation remains constant as the particle size changes. Teva Br. at 10. Teva asserts that because the 1.3 micron figure is expressly disclosed in the patent, it provides the best guide to the meaning of the term "about" as that term is used to refer to measurement variability around a mean.

Teva applies a different methodology for constructing the term "about" as it is used with respect to 90th-percentile values. Teva asserts that the 1.3 micron standard deviation disclosed in the patents applies only to *mean* particle sizes, and that the patents disclose no methodology or data for the "90% less than" value. Accordingly, Teva and Dr. Kibbe employ a simple rounding methodology to interpret the term "about" when the patents specify that 90% of the particles must measure "less than *about* 50 microns" – that is, "a particle cannot be larger than 50.4 microns and still round down to 50

microns." Defs.' Ex. D (Kibbe Report) ¶ 29. Using these two methodologies – application of a 1.3-micron standard deviation to mean values, and a rounding methodology to 90th-percentile values – Teva proposes the constructions denoted in the table, *supra*.

Lilly disputes Teva's approach, arguing that its use of two methodologies is internally inconsistent, as well as contradicted by industry standards (as reflected by the USP) and by Teva's own practices in measuring raloxifene particles. Lilly faults Teva's standard deviation method for "treat[ing] the standard deviation as an absolute quantity divorced from the reference measured value, resulting in some cases in a degree of variability that is too large and in others too small[,]" and noting that the use of one standard deviation as the allowance of error is the equivalent of applying a 68% confidence interval. Lilly Br. at 21-22. Lilly also criticizes Teva's rounding methodology as arbitrary and inconsistent with the patent specification. Further, Lilly provides evidence that Teva's real-world practice of measuring raloxifene particles involves application of the coefficient of variation (or relative standard deviation), just as Lilly proposes, and unlike the methods proposed by Teva in this litigation. Pls.' Ex. 11 at T00125-27.

Analysis

We note, first, that the range denoted by the term "about" is to be "interpreted in its technological and stylistic context." Central Admixture Pharmacy Servs., Inc. v.

Advanced Cardiac Solutions, PC, 482 F.3d 1347, 1355 (Fed. Cir. 2007); see also Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211, 1217 (Fed. Cir. 1995) (noting that "the word 'about' does not have a universal meaning in patent claims, and . . . the meaning depends on the technological facts of the particular case."). Accordingly, we construe the term "about" based on the specific circumstances and patent claims in this case.

Teva is correct that, in construing patent terms, intrinsic evidence is of paramount importance and primary focus. See Atofina v. Great Lakes Chemical Corp., 441 F.3d 991, 996 (Fed. Cir. 2006). However, Teva's assertion – that, because a 1.3 micron control sample standard deviation is disclosed in the patents, this figure must represent the degree of measurement variability denoted by "about" – misconstrues, in our view, this canon. Nowhere do the patents specify that the 1.3 micron figure is meant to constitute the "entire answer" to the measurement variability question, and, based on our reading of the patent and the evidence presented by both parties, we do not think it does so. Further, Lilly explains how this figure fits within the calculations it uses to support its proposed constructions of the term "about" (as described in footnote 12, *supra*).

Teva's argument on this point is unpersuasive for the additional reason that it utilizes two completely different methodologies in proposing claim constructions for the two different instances of "about" in the patents. The Federal Circuit has held that "[a] claim term used in multiple claims should be construed consistently." Inverness Medical Switzerland GmbH v. Princeton Biomeditech Corp., 309 F.3d 1365, 1371 (Fed. Cir. 2002); see also Gillespie v. Dywidag Systems Int'l, USA, 501 F.3d 1285, 1291 (Fed. Cir.

2007); Phillips v. AWH Corp., 415 F.3d 1303, 1314 (Fed. Cir. 2005). While Lilly uses a slight variation in its computations (the difference in the CV value, from 10% to 15%) for mean measurements and 90th-percentile measurements, based on standard statistical principles in line with USP protocol, it uses the same core methodology for construing each "about" term. In contrast, Teva's two methodologies for measuring variability – application of the control sample standard deviation for mean measurements, and rounding for 90th-percentile measurements – are completely different. Teva's proposed constructions are thus internally inconsistent, and neither methodology, in our judgment, is supported by the evidence.

Teva's arguments that Dr. Thisted is unqualified to opine as an expert in the pharmaceutical formulations field are also not well-taken. We have no doubt that Dr. Thisted is qualified to testify as an expert as to the issues presented here; his education and professional experience regarding the application of statistical measurements in the pharmaceutical formulation context are clearly relevant. In addition, as Lilly points out, Dr. Thisted has previously appeared and testified in this Court as an expert statistician in the pharmaceutical field, and advises pharmaceutical companies regarding submissions to the FDA. See, e.g., Eli Lilly and Co. v. Zenith Goldline Pharms., Inc., 364 F. Supp. 2d 820 (S.D. Ind. 2005) (Young, J.); Pl.'s Exs. 24, 33.

Moreover, the statistical techniques proposed by Dr. Thisted do not strike us as so arcane or specialized as Teva characterizes them. The parties here (and any party with the skills and knowledge to measure particles and formulate pharmaceuticals using the

methods disclosed in the patents) are clearly sophisticated and highly skilled. The complexity of the techniques disclosed in the patents belies Teva's assertion that the statistical measures proposed by Lilly are outside the purview of a person of ordinary skill in the art of pharmaceutical formulation. Thus, we adopt Lilly's proposed constructions of these five claim terms.[17]

Conclusion

For the reasons detailed above, we conclude that the proper constructions of the disputed terms of the Lilly patents at issue are as follows:

Disputed Term	**Court's Construction**
surfactant	A compound that reduces the surface tension of liquids, or reduces interfacial tension between two liquids or a liquid and a solid.
water-soluble diluent	A pharmaceutically inert substance, capable of being dissolved in water, that increases the bulk of a tablet.
size	The equivalent spherical volume diameter of a particle as determined by laser light diffraction scattering.
mean particle size	Mean equivalent spherical volume diameter by laser light diffraction scattering.
less than about 25 microns	A measured value of less than **30.1** microns.
less than about 50 microns	A measured value of less than **67.4** microns.
between 5 and about 20 microns	A measured value between 5 microns and **24.1** microns.

[17] In its claim construction brief, Lilly includes the following sentence in each of its proposed constructions in this category: "The term 'about' means values within the reasonably expected range of variability in the measurement process." We omit this verbiage as extraneous.

between about 5 and about 25 microns	A measured value between **4.0** microns and **30.1** microns.
between about 5 and about 20 microns	A measured value between **4.0** microns and **24.1** microns.

IT IS SO ORDERED.

Date: 06/11/2008

SARAH EVANS BARKER, JUDGE
United States District Court
Southern District of Indiana

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